Remarks

In this response, Applicants have cancelled claims 1 to 26 without prejudice and added new claims 27-47. Support for new claims can be found throughout the specification and in particular on page 2, lines 4 to 11, page 6, lines 20 to 27, page 8 to page 10, and in Examples 1 and 2.

REJECTION UNDER 35 U.S.C. § 112 SECOND PARAGRAPH

Claims 1-26 stand rejected under 35 U.S.C. § 112 second paragraph as failing to distinctly point out the subject matter of the invention. The Examiner states that the claims are indefinite because the acronym "GLP-1" is not spelled out with sufficient meaning to convey what the applicant intends to be the claimed invention. Applicants have submitted new claims to spell out the acronym. The specification states, "Glucagon-like peptide-1 (7-37)-OH (GLP-1) is a 31 amino acid hormone that is produced by post-translational processing of the preglucagon gene product in the brain, stomach, intestine, and pancreas." (Applicants' specification, page 2). Additionally, the new claims further define the GLP-1 molecules contemplated by the invention by specified GLP-1 formulas. Thus, Applicants respectfully submit that the metes and bounds of the claim are clear and request the §112 second paragraph rejection be withdrawn.

REJECTION UNDER 35 U.S.C. § 102

Claims 1-2, 4, 6-10, 14-18, 22-23 and 24-25 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Jensen et al. (WO 96/20005, July 15, 1996). To put the claims in allowable format, Applicants have submitted new independent claims to expressly state that the formulation is a solution. Jensen et al. teaches a composition that results in a gel which shows protracted release of the GLP-1 compound and not a solution formulation.

Claims 1-2, 4, 6-10, 14-18, 22 and 24 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Andrews et al. (WO 93/25579, December 23, 1993). Applicants respectfully disagree with the Examiner's assertion that the limitations of the claimed invention are met by the reference. The Examiner admits that the reference does not teach the recited pH range as claimed by the Applicants. However, the Examiner asserts that because the structure of the claimed peptide is the same as SEQ ID NOS: 2 and 3, then the

pH is considered to be an inherent property. The pH is not an inherent property of the molecule. Other pH ranges may allow one to resuspend and assay the GLP-1 molecule, but may not provide chemical and physical stability. The pH provided in the claimed invention contributes to the shelf stable solution formulation and is not found in or inherent from the cited reference.

REJECTION UNDER 35 U.S.C. § 103

The subject matter of the claims was commonly owned at the time the invention was made.

Claims 1-26 stand rejected under 35 U.S.C. § 103 as being unpatentable over Smith et al. (U.S. Patent No. 5,908,830, October 30, 1997) in view of Jensen et al. (WO 96/20005, July 15, 1996). The Examiner states that the Smith reference teaches the use of TRIS buffer at pH 8 in combination therapy for the treatment of diabetes and the Jensen reference teaches GLP-1 compounds that have protracted action, a preservative, a tonicity modifier that is glycerol, and a pH of 8.7. Applicants request reconsideration and withdrawal of the rejection.

To support a *prima facie* case of obviousness over a combination of prior art references, the Examiner must establish that the prior art contains a suggestion or motivation to combine the prior art references in such a way as to achieve the claimed invention. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). The Federal Circuit has also in several cases stated that hindsight is not a justifiable basis on which to find an invention obvious. *See In re Dembiczak*, 175 F.3d 994 (Fed. Cir. 1999). To avoid a hindsight analysis wherein the inventor's teachings are used against him, "there must be a rigorous application of the requirement for showing the teaching or motivation to combine the prior art references." *Id.* at 999.

In this case, the cited references do not explicitly or implicitly teach, suggest, or motivate a skilled person to combine the references and arrive at the invention without using Applicants' specification. As previously mentioned, the Jensen reference actually provides examples of achieving a gel formulation of GLP-1 for protracted delivery. The Smith reference relates generally to a combination therapy and does not suggest a shelf stable solution formulation at the claimed pH range. Tris buffer at pH 8 is not found in claims 3, 11, or 19 of the Smith reference but rather, is found only in Example 1 and it is used to

resuspend OB protein. It does not mention the buffer or pH as being useful for a shelf stable formulation of GLP-1 molecules. Applicants' formulation overcomes physical and chemical stability issues. As stated in the specification, "Physical stability refers to properties such as protein aggregation, which can be measured by a sample's attenuation of light. The measurement relates to the turbidity of a formulation. Turbidity is produced by aggregation or precipitation of proteins or complexes in the formulation and is indicative of decreased stability of a solution formulation. The more turbid a protein preparation, the less stable the preparation is. Stability also refers to the chemical stability of the formulation such as the propensity of the proteins to form high order polymers which is indicative of decreased stability." (Applicants' specification, page 4). The claimed formulation reflects a reduction in turbidity caused by aggregation or precipitation as well as the formation of high order polymers of the GLP-1 compound. The cited references alone or in combination do not provide a shelf stable solution formulation. Thus, a case of obviousness cannot be supported.

SUMMARY AND CONCLUSION

Applicants respectfully assert that the application is now in condition for allowance. The claims are definite and particularly point out and distinctly claim the subject matter being sought. The shelf stable solution formulation is neither anticipated nor obvious in view of the cited references. If, for any reason, the Examiner feels that a telephone conversation would be helpful in expediting the prosecution of this case, the Examiner is urged to call me.

Respectfully submitted,

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